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ORIGINAL RESEARCH

Gustave Roussy Immune Score Predicts Outcomes in Hepatocellular Carcinoma Treated with TACE and Immunotherapy

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Objective: To evaluate the prognostic value of the Gustave Roussy Immune (GRIm) score and the hepatocellular carcinoma–specific GRIm (HCC-GRIm) score in unresectable hepatocellular carcinoma (uHCC) treated with transarterial chemoembolization (TACE) plus immune checkpoint inhibitors (ICIs) and anti-VEGF antibodies/tyrosine kinase inhibitors (TKIs), and to examine their association with hepatitis B virus (HBV) activation and immune markers.

Methods: This retrospective study enrolled uHCC patients receiving TACE plus ICIs and anti-VEGF antibodies/TKIs. Baseline blood tests were used to calculate GRIm and HCC-GRIm scores and determine HBV activation (HBV DNA > 60 IU/mL). Patients were stratified by GRIm, HCC-GRIm, and HBV activation. Objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and peripheral immune markers were compared across groups. Cox regression identified independent prognostic factors, and the prognostic value of key predictors was compared with Barcelona Clinic Liver Cancer (BCLC) and China Liver Cancer (CNLC) staging systems.

Results: Sixty-seven patients were included. ORR and DCR were 53.7% and 86.6%; median OS was 30.4 months. High GRIm and HCC-GRIm scores were associated with shorter OS than low scores (GRIm: 15.4 vs 34.0 months, $P = 0.019$; HCC-GRIm: 15.4 vs 36.7 months, $P = 0.002$). OS and response did not differ significantly by HBV activation within score strata. Igλ, Igκ, and IgG levels were higher in patients with elevated GRIm/HCC-GRIm scores (all $P < 0.01$). ECOG performance status, GRIm, HCC-GRIm, and $CD3^+CD8^+$ proportion were independent prognostic factors, and $CD3^+CD8^+$ stratification showed better OS discrimination than GRIm, HCC-GRIm, BCLC, and CNLC.

Conclusion: GRIm and HCC-GRIm are effective prognostic indicators in uHCC patients treated with TACE plus ICIs and anti-VEGF antibodies/TKIs, reflecting systemic immune and inflammatory status. Both scores retain prognostic value regardless of pre-treatment HBV activation but do not predict tumor response. In this single-center cohort, GRIm provided prognostic discrimination comparable to HCC-GRIm, and $CD3^+CD8^+$ T-cell stratification also showed prognostic value, offering an additional approach for risk assessment. Future larger, multicenter studies are needed to validate these findings and to define the optimal roles of GRIm, HCC-GRIm, and $CD3^+CD8^+$-based stratification in routine clinical practice.

Keywords: GRIm score, HCC-GRIm score, hepatocellular carcinoma, TACE, prognosis, immune microenvironment

Introduction

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related morbidity and mortality worldwide, with nearly half of new cases and deaths occurring in China each year.[1] While surgical resection offers favorable outcomes for early-stage disease, most patients are diagnosed at intermediate or advanced stages, and a substantial proportion present with unresectable HCC (uHCC), precluding curative treatment.[1] For intermediate-stage HCC, transarterial chemoembolization

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(TACE) remains the standard locoregional therapy, whereas immune checkpoint inhibitors (ICIs) combined with anti–vascular endothelial growth factor (VEGF) antibodies or tyrosine kinase inhibitors (TKIs) have become the main systemic option for advanced or unresectable disease.[2] Recent Phase III trials and real-world studies, including LEAP-012, CARES-005 and the CHANCE series, consistently indicate that integrating TACE with ICIs and anti-angiogenic agents improves progression-free survival, overall survival, and objective response compared with TACE alone.[2–6]

Despite these advances, substantial prognostic heterogeneity persists among patients with uHCC, highlighting the need for robust tools to guide individualized treatment.[7] The Gustave Roussy Immune (GRIm) score, originally developed to stratify patients receiving immunotherapy, integrates the neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), and serum albumin as composite markers of systemic inflammation and immune status.[8] GRIm has demonstrated prognostic value across multiple malignancies, and its HCC-adapted version (HCC-GRIm) further incorporates liver function parameters to improve specificity in this setting.[9–11] However, the prognostic significance of GRIm and HCC-GRIm in uHCC patients receiving combination regimens such as TACE plus ICIs and anti-VEGF antibodies/TKIs has not been systematically evaluated, despite their close conceptual link to the heterogeneous tumor immune microenvironment in HCC.[12] In parallel, hepatitis B virus (HBV) infection, the leading cause of HCC in Asia, profoundly reshapes the immune microenvironment and may influence responses to immunotherapy.[13] Although prior trials suggest survival benefits of ICI-based combinations in HBV-positive patients, emerging data point to marked immune heterogeneity within this population, particularly in the context of active viral replication and low-level viremia.[14–16] Given that GRIm-based scores reflect systemic immune–inflammatory status, pre-treatment HBV activation may modify peripheral immune profiles and affect the prognostic performance of GRIm and HCC-GRIm, making it essential to evaluate this interaction in HBV-related uHCC treated with combination therapy.

Therefore, this study aims to systematically evaluate the prognostic value of the GRIm score and HCC-GRIm score in patients with uHCC undergoing TACE in combination with ICIs and anti-VEGF antibodies or TKIs. Additionally, the study seeks to characterize the peripheral immune profiles associated with different GRIm score levels and to explore the potential impact of pre-treatment HBV activation status on the applicability and prognostic performance of these scoring systems, in order to provide a new reference for the individualized treatment of uHCC.

Materials and Methods

Patient Selection

This retrospective study was approved by the Institutional Review Board and the Ethics Committee. Since the study was retrospective, informed consent was not required. From July 1, 2018, to July 1, 2024, patients with uHCC who underwent TACE plus ICIs and anti-VEGF antibodies/TKIs were included. The eligibility criteria for patient inclusion were as follows: (1) a diagnosis of HCC confirmed either histologically or clinically, in accordance with the American Association for the Study of Liver Diseases (AASLD) guidelines; (2) Barcelona Clinic Liver Cancer (BCLC) stage B or C; (3) liver function classified as Child-Pugh class A or B, with no evidence of uncontrollable ascites or hepatic encephalopathy; (4) an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; (5) receipt of combination therapy involving TACE, ICIs, and anti-VEGF antibodies or TKIs. The combination therapy was defined as either the concurrent administration of initial TACE and the first ICI dose, or initiation of ICI therapy within one months following TACE. TKIs were administered concurrently with either TACE or ICIs. Additionally, at least four cycle of ICI treatment was required post-TACE.

Patients were excluded based on the following criteria: (1) histologically confirmed non-pure HCC, including intrahepatic cholangiocarcinoma (ICC), combined hepatocellular–cholangiocarcinoma, sarcomatoid hepatocellular carcinoma, or fibrolamellar hepatocellular carcinoma; (2) presence of concurrent malignancies other than HCC; (3) previous exposure to systemic therapies including immune checkpoint inhibitors, anti-VEGF agents, TKIs, or conventional chemotherapy; (4) absence of key hematologic or immunologic data, rendering outcome analysis unfeasible and preventing the calculation of GRIm and HCC-GRIm scores; (5) a follow-up duration of less than three months following initiation of the combination treatment.

Relevant Definitions

GRIm score was calculated by serum albumin level (< 3.5 g/dL = 1 point), serum LDH level (> 220 U/L = 1 point) and serum NLR (> 6 = 1 point). Patients with a total score of 0~1 were classified as the low GRIm group, while those with 2~3 points were classified as the high GRIm group. The HCC-GRIm score was calculated by adding aspartate aminotransferase (AST) / alanine aminotransferase (ALT) (≥1.44 = 1 point) and total bilirubin level (≥1.3 mg/dl = 1 point) in addition to these parameters. Patients with a total score of 0~2 were classified as the low HCC-GRIm group, and those with 3~5 points were classified as the high HCC-GRIm group. HBV activation was defined as a serum HBV DNA level > 60 IU/mL in HBsAg-positive patients, corresponding to the lower limit of quantification of our real-time PCR assay and considered clinically significant in line with previous studies on low-level viremia and virologic response.[16]

Overall survival (OS) was defined as the interval from the time of diagnosis to either death from any cause or the last follow-up for patients who remained alive. Progression-free survival (PFS) was defined as the time from diagnosis to the occurrence of disease progression or death, whichever occurred first. The survival data for all patients were last updated in January 2025. The initial treatment efficacy and tumor response were first assessed at the fourth cycle or the end of the third month according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).[17] Classify all patients into progressive disease (PD), stable disease (SD), and objective response (OR; including partial response [PR] and complete response [CR]) groups based on the first evaluation.

TACE Procedure

All TACE procedures were conducted by two interventional radiologists, each with over 10 years of clinical experience. Pirarubicin was used as the intra-arterial chemotherapeutic agent during all TACE procedures. To minimize procedural variability and enhance embolization efficacy, a precision TACE approach was employed.[18] The application of subsequent "on-demand" TACE sessions (typically evaluated after 3~4 treatment cycles) was determined based on tumor marker dynamics and imaging assessments. The continuation of TACE was halted if any of the following criteria were met: (1) deterioration to Child-Pugh class C, indicated by factors such as refractory ascites, severe jaundice, overt hepatic encephalopathy, or hepatorenal syndrome; (2) an Eastern Cooperative Oncology Group (ECOG) performance status greater than 2; (3) persistent progression of target lesions after three TACE treatments, as evaluated by the mRECIST.

ICIs and Anti-VEGF Antibodies/TKIs Administration

All patients enrolled in this study received a combination regimen of ICIs with either anti-VEGF antibodies or TKIs, all of which were approved by the National Medical Products Administration and commercially available in China. The ICIs administered in this cohort included camrelizumab and sintilimab. Anti-VEGF therapy consisted of bevacizumab, which was given concurrently with ICIs. For patients receiving oral TKIs, including lenvatinib and sorafenib, treatment was temporarily suspended for 2–3 days before and after each TACE session to reduce the risk of procedure-related complications. All therapeutic agents were administered according to their recommended dosages and schedules, following national guidelines and local clinical practice. The administration of ICIs and anti-VEGF antibodies or TKIs continued until either radiological disease progression or the emergence of intolerable adverse events.

Molecular targeted agents (TKIs or anti-VEGF antibodies) were administered at their standard recommended doses and schedules. Oral TKIs were temporarily interrupted for two days before and after each TACE session if no significant post-procedural symptoms occurred. Dose reductions for TKIs and anti-VEGF agents were permitted according to product labels and clinical judgment to manage treatment-related adverse events (AEs). ICIs were administered at standard doses and frequencies, with no dose reduction allowed. However, temporary interruption of ICIs was permitted in cases of immune-related AEs ≥ grade 2 and resumed when toxicity resolved to grade ≤1, with a maximum interruption period of 12 weeks. TKIs were paused for grade ≥2 AEs, such as hypertension, proteinuria, or hand–foot skin reaction, and reintroduced at the same or a reduced dose upon recovery. All adjustments adhered to established clinical protocols and were individualized based on patient tolerance and organ function. Adverse events were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.[19]

Follow-Up

The primary outcomes of this study were ORR and DCR-assessed at the first treatment evaluation. Secondary outcomes included OS, PFS and AEs. AEs were evaluated according to CTCAE v5.0. Following the initiation of combination therapy, patients underwent follow-up assessments every 6 to 9 weeks. These evaluations included imaging studies and laboratory tests. Imaging assessments comprised contrast-enhanced abdominal MRI and chest–abdomen CT scans, in which non-contrast CT components were used solely to evaluate extrahepatic disease. Tumor response according to mRECIST was assessed on contrast-enhanced dynamic liver MRI or multiphasic contrast-enhanced liver CT. Laboratory analyses included complete blood counts, comprehensive biochemical profiles, tumor marker measurements, HBV-DNA quantification, cytokine profiling, immune status assessments, chest pain panels, and thyroid function tests. ICIs were administered at three-week intervals, with pre-treatment laboratory evaluations conducted prior to each cycle, covering hematologic parameters, biochemical tests, immune indices, chest pain panels, and thyroid function assessments. Tumor response was determined in accordance with the mRECIST.

Peripheral Immune Markers

Peripheral blood samples were collected prior to TACE. Immune profiling included the assessment of lymphocyte subsets, specifically the percentages of $CD3^+$ T cells, $CD3^+CD4^+$ helper T cells, $CD3^+CD8^+$ cytotoxic T cells, $CD3^-CD16^+56^+$ natural killer (NK) cells, and $CD3^-CD19^+$ B cells, along with the $CD4^+/CD8^+$ ratio. Additional immunological parameters measured included immunoglobulin λ (Igλ), immunoglobulin κ (Igκ), complement components C3 and C4, immunoglobulin classes M (IgM), A (IgA), and G (IgG), as well as complement factor B (CFB). All immune-related and hematologic parameters were comprehensively recorded at baseline (prior to the initiation of combination therapy).

Peripheral blood mononuclear cells (PBMCs) were isolated via density gradient centrifugation using the Ficoll-Paque method and resuspended at a concentration of $1\times10^{\wedge6}$ cells/mL. Flow cytometric analysis of PBMCs was performed using a FACScan Caliber system (Becton Dickinson, Franklin Lakes, NJ, USA). Serum immunoglobulin levels and complement components were quantified using the immune turbidimetric assay, while NLR was calculated from routine complete blood count results.

Statistical Analysis

All analyzes were performed using the SPSS 23.0 program. Continuous variables are expressed as means with 95% confidence intervals. For categorical variables, counts and percentages are presented. Shapiro–Wilk tests were performed to determine the normality of the data distribution. For data that followed a normal distribution, significance testing for differences was conducted using either the chi-square test or the two-tailed paired Student's *t*-test. For data that did not follow a normal distribution, the Kruskal–Wallis test or the nonparametric Mann–Whitney *U*-test was used to test for significant differences. factors predicting survival. OS was estimated by the Kaplan–Meier method and Log rank test. Prognostic factors for OS were evaluated in univariate and multivariable Cox regression models. A logistic regression model was created with variables with a p-value of <0.05, and independent factors predicting overall survival were identified.

Results

Patient Characteristics

From July 1, 2018, to July 1, 2024, a total of 187 uHCC patients undergoing TACE plus ICIs and anti-VEGF antibodies/TKIs were screened. Finally, 67 patients with complete follow-up data who met the inclusion criteria were enrolled. The patient enrollment and selection process, including inclusion and exclusion criteria, is depicted in the flow diagram (Figure 1). The characteristics of each group are summarized in Table 1. Prior to treatment, HBV activation was observed in 26 patients (38.8%), while 41 patients (61.2%) showed no evidence of HBV activation. Based on the GRIm score, 50 patients (74.6%) were classified into the low-score group (0–1), and 17 patients (25.4%) were classified into the high-

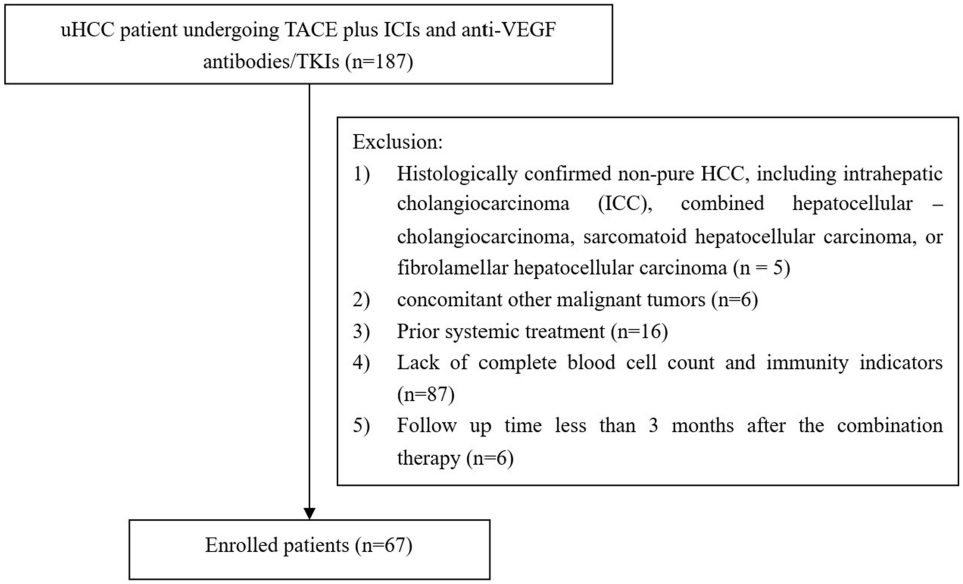

Figure 1 Flowchart of study enrollment.

score group (2–3). According to the HCC-GRIm score, 47 patients (70.1%) were categorized as low (0–2), while 20 patients (29.9%) were categorized as high (3–5).

Efficacy and Safety

At the first evaluation, the (ORR reached 53.7%, and the DCR was 86.6%. By the time of the last follow-up on January 1, 2025, the median follow-up duration for the entire study population was 18.2 months (interquartile range

Table 1 Demographic Characteristics of Patients

	N (%), 67 (100)
Age (median) (min-max)	59 (33–77)
Sex	
Female	12 (17.9)
Male	55 (82.1)
Comorbidite	
Yes	25 (37.3)
No	42 (62.7)
ECOG PS	
0	36 (53.7)
1	31 (46.3)
BCLC Stage	
B	33 (49.2)
C	34 (50.8)
CNLC Stage	
II	32 (47.8)
III	35 (52.2)
Child Pugh Score	
A	55 (82.1)
B	12 (17.9)

(*Continued*)

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Table 1 (Continued).

	N (%), 67 (100)
MELD score	6.0 (3.8, 8.0)
Pre-treatment HBV activation	
Yes	26 (38.8)
No	41 (61.2)
AFP>400 (ug/L)	
Yes	24 (35.8)
No	43 (64.2)
Abnormal prothrombinm (mAU/mL)	1236.75 (95.31, 7640.74)
Extrahepatic spread	
Yes	18 (26.9)
No	49 (73.1)
Vascular invasion	
Yes	25 (37.3)
No	42 (62.7)
CA19-9 (IU/mL)	9.06 (4.99, 16.25)
$CD3^{-}CD(16^{+}56)^{+}$ (%)	14.37 (11.01, 21.59)
$CD3^{+}$ (%)	73.65 (67.69, 78.85)
$CD3^{+}CD4^{+}$ (%)	39.77 (36.25, 47.64)
$CD3^{+}CD8^{+}$ (%)	25.89 (21.01, 32.25)
$CD4^{+}/CD8^{+}$ (%)	1.49 (1.15, 2.12)
$CD3^{-}CD19^{+}$ (%)	9.01 (6.09, 13.05)
Igλ (mg/dl)	603.00 (474.00, 844.00)
Igκ (mg/dl)	1110.00 (928.00, 1495.00)
IgM (g/L)	1.05 (0.75, 1.61)
IgA (g/L)	2.92 (2.54, 3.91)
IgG (g/L)	13.30 (10.50, 17.20)
C3 (g/l)	0.86 (0.74, 1.02)
C4 (g/l)	0.20 (0.16, 0.24)
CFB (mg/dl)	42.90 (35.05, 53.80)
Alkaline phosphatase (U/L)	111.7 (87.85, 159,2)
GRIm score	
Low (0–1)	50 (74.6)
High (2–3)	17 (25.4)
HCC-GRIm score	
Low (0–2)	47 (70.1)
High (3–5)	20 (29.9)

Abbreviations:: ECOG, Eastern Cooperative Oncology Group; BLCL, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; MELD, model for end-stage liver disease score; HBV, hepatitis B virus; AFP, Alpha-fetoprotein; GRIm, Gustave Roussy Immune; HCC-GRIm, hepatocellular carcinoma-specific Gustave Roussy Immune.

[IQR]: 11.5–29.9 months). The cohort exhibited a mOS of 30.4 months (95% confidence interval [CI]: 18.5–34.9 months) and a mPFSof 11.0 months (95% CI: 8.6–12.9 months).

AEs observed during the study were generally mild and manageable, with no treatment-related deaths recorded. The overall incidence of AEs was 59.7% (40 out of 67 patients), with the most common events being fever (56.7%), abdominal pain (46.3%), liver function abnormalities (19.4%), hand-foot skin reaction (22.4%), hypertension (14.9%), thrombocytopenia (9.0%), proteinuria (16.4%), and immune-related myocarditis (1.5%).

Clinical Characteristics

There were significant differences in HBV activation status and ALP levels between different GRIm and HCC-GRIm score groups. In the GRIm stratification, patients with high GRIm scores had a higher rate of HBV activation compared to those with low GRIm scores (64.7% vs 30.0%, $P = 0.020$). A comparable pattern was observed in the HCC-GRIm classification, with HBV activation present in 60.0% of patients in the high-score group, significantly higher than the 29.8% observed in the low-score group ($P = 0.029$). Furthermore, ALP levels were significantly elevated in patients with higher GRIm scores [median 138.10 U/L (IQR: 106.80–258.70)] relative to those with lower scores [median 108.45 U/L (IQR: 83.67–151.30), $P = 0.026$]. Similarly, the high HCC-GRIm score group demonstrated increased ALP levels [median 143.45 U/L (IQR: 105.85–233.88)] compared to the low-score group [median 108.10 U/L (IQR: 82.85–140.50), $P = 0.012$, Table 2].

Peripheral Immune Markers

Peripheral immune markers, including Igλ, Igκ, and IgG, were significantly elevated in patients with higher GRIm and HCC-GRIm scores. Igλ, Igκ, and IgG levels were all significantly higher in the high GRIm group compared to the low

Table 2 Patient Characteristics According to GRIm Score and HCC-GRIm Score

Variable	GRIm score			HCC-GRIm score		
	Low	High	*P*	Low	High	*P*
Age (y)	56 (62,67)	53 (55,64)	0.131	58 (62,66)	49 (55,64)	0.067
Sex			0.072			0.182
Female	44 (88.0)	11 (64.7)		41 (87.2)	14 (70.0)	
Male	6 (12.0)	6 (35.3)		6 (12.8)	6 (30.0)	
Comorbidite			0.285			0.279
Yes	21 (42.0)	4 (23.5)		20 (42.6)	5 (25.0)	
No	29 (58.0)	13 (76.5)		27 (57.4)	15 (75.0)	
ECOG PS			0.721			0.895
0	28 (56.0)	8 (47.1)		26 (55.3)	10 (50.0)	
1	22 (44.0)	9 (52.9)		21 (44.7)	10 (50.0)	
BCLC Stage			1.000			0.851
B	25 (50.0)	8 (47.1)		24 (51.1)	9 (45.0)	
C	25 (50.0)	9 (52.9)		23 (48.9)	11 (55.0)	
CNLC Stage			0.728			0.574
II	25 (50.0)	7 (41.2)		24 (51.1)	8 (40.0)	
III	25 (50.0)	10 (58.8)		23 (48.9)	12 (60.0)	
Child Pugh Stage			0.287			0.182
A	43 (86.0)	12 (70.6)		41 (87.2)	14 (70.0)	
B	7 (14.0)	5 (29.4)		6 (12.8)	6 (30.0)	
MELD score	6.00 (4.00, 7.15)	7.00 (3.00, 8.00)	0.942	6.00 (3.90, 7.10)	6.90 (3.00, 8.00)	0.768
Pre-treatment HBV activation			0.020			0.029
Yes	15 (30.0)	11 (64.7)		14 (29.8)	12 (60.0)	
No	35 (70.0)	6 (35.3)		33 (70.2)	8 (40.0)	
Extrahepatic spread			1.000			1.000
Yes	13 (26.0)	5 (29.4)		13 (27.7)	5 (25.0)	
No	37 (74.0)	12 (70.6)		34 (72.3)	15 (75.0)	
Vascular invasion			0.843			0.567
Yes	18 (36.0)	5 (29.4)		16 (34.0)	9 (45.0)	
No	32 (64.0)	12 (70.6)		31 (66)	11 (55.0)	
CA19-9 (IU/mL)	8.70 (4.92, 15.30)	11.76 (6.09, 19.58)	0.420	8.34 (4.72, 15.06)	11.71(6.11, 20.24)	0.330
AFP>400 (ug/L)			1.000			0.852
Yes	18 (36.0)	6 (35.3)		16 (34.0)	8 (40.0)	
No	32 (64.0)	11 (64.7)		31 (66.0)	12 (60.0)	
Abnormal prothrombinm (AU/mL)	989.75 (100.94, 7010.16)	2150.46 (58.99, 8213.76)	0.550	964.14 (95.31, 6569.44)	2070.96 (91.57, 8796.01)	0.423
Alkaline phosphatase (U/L)	108.45 (83.67, 151.30)	138.10 (106.80, 258.70)	0.026	108.10 (82.85, 140.50)	143.45 (105.85, 233.88)	0.012

Abbreviations:: ECOG, Eastern Cooperative Oncology Group; BLCL, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; MELD, model for end-stage liver disease score; HBV, hepatitis B virus; AFP, Alpha-fetoprotein.

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GRIm group (P = 0.016, 0.006, and 0.008, respectively). Similar differences were observed in the HCC-GRIm stratification, with higher levels of these immune indicators in the high-score group (P = 0.002, 0.001, and 0.001, respectively; Table 3).

Survival Assessment

GRIm score: In the unstratified analysis, patients with high GRIm scores demonstrated shorter OScompared to those with low GRIm scores [median OS: 15.4 months (95% CI: 9.6–28.3) vs 34.0 months [95% CI: 23.8–Not Reached (NR)], P = 0.019]. In the stratified analysis based on HBV activation status, no significant difference in OS was observed between patients with and without HBV activation in either the low GRIm group (P = 0.624) or the high GRIm group (P = 0.134, Figure 2).

HCC-GRIm score: For the HCC-GRIm classification, patients with high scores had significantly reduced OS compared to those with low scores [median OS: 15.4 months (95% CI: 8.1–28.3) vs 36.7 months (95% CI: 23.8–NR), P = 0.002]. In the stratified analysis of HCC-GRIm scores, no significant difference in OS was found between patients with and without HBV activation in either the low HCC-GRIm group (P = 0.724) or the high HCC-GRIm group (P = 0.053, Figure 2).

Tumor Response

At best response, no significant differences were observed between low and high GRIm score groups in terms of PD, SD, and OR rates (P = 0.181). Similar results were found between the low and high HCC-GRIm groups (P = 0.250). At the first evaluation, tumor response patterns (PD, SD, OR) also did not differ significantly between GRIm score groups (P = 0.484) or HCC-GRIm score groups (P = 0.131, Table 4). Tumor response stratified by HBV activation showed no significant differences between HBV activation and non-activation subgroups in either GRIm or HCC-GRIm score groups (all $P > 0.05$, Table 5).

Prognostic Factors for OS

In univariate analysis, ECOG performance score, Vascular invasion, $CD3^+CD8^+$, Igκ, IgA, GRIm score and HCC-GRIm score were significant prognostic variables for OS ($P < 0.05$). In multivariate analysis, ECOG performance score, $CD3^+CD8^+$, GRIm score and HCC-GRIm score were independent for OS was prognostically variable ($P < 0.05$, Table 6).

Table 3 Peripheral Immune Markers According to GRIm Score and HCC-GRIm Score

Variable	GRIm score			HCC-GRIm score		
	Low	High	P	Low	High	P
$CD3^-CD(16^+56)^+$ (%)	13.57 (8.66, 20.30)	18.47 (12.51, 24.38)	0.150	13.15 (7.91, 20.77)	17.80 (14.00, 23.88)	0.148
$CD3^+$ (%)	74.57 (67.94, 81.22)	74.10 (69.09, 80.81)	0.741	74.38 (67.28, 81.47)	70.91 (67.70, 76.61)	0.387
$CD3^+CD4^+$ (%)	41.00 (37.92, 47.77)	36.88 (34.09, 46.30)	0.243	40.90 (37.97, 47.34)	38.00 (34.08, 49.37)	0.466
$CD3^+CD8^+$ (%)	26.76 (20.79, 32.26)	24.97 (22.36, 31.67)	0.965	26.91 (21.01, 32.25)	24.80 (21.18, 32.06)	0.809
$CD4^+/CD8^+$ (%)	1.54 (1.17, 2.15)	1.44 (1.08, 1.79)	0.485	1.49 (1.17, 2.03)	1.46 (1.07, 2.42)	0.681
$CD3^-CD19^+$ (%)	8.48 (5.80, 13.06)	9.70 (6.77, 12.48)	0.660	8.69 (5.89, 13.05)	9.36 (6.76, 12.71)	0.811
Igλ (mg/dl)	572.50 (452.00, 764.25)	703.00 (618.00, 1010.00)	0.016	570.00 (449.50, 741.50)	730.50 (620.25, 1012.50)	0.002
Igκ (mg/dl)	1035.00 (840.00, 1432.50)	1390.00 (1130.00, 1620.00)	0.006	996.00 (834.50, 1375.00)	1410.00 (1167.50, 1632.50)	0.001
IgM (g/l)	0.93 (0.72, 1.56)	1.14 (1.02, 1.63)	0.185	0.92 (0.71, 1.55)	1.18 (1.02, 1.61)	0.148
IgA (g/l)	2.85 (2.51, 3.77)	3.33 (2.66, 4.12)	0.286	2.81 (2.42, 3.56)	3.51 (2.71, 4.14)	0.060
IgG (g/l)	12.05 (10.12, 16.80)	15.20 (13.40, 17.90)	0.008	11.90 (10.04, 16.60)	16.00 (13.62, 18.72)	0.001
C3 (g/l)	0.85 (0.74, 0.99)	1.00 (0.73, 1.11)	0.208	0.86 (0.74, 0.99)	0.88 (0.74, 1.11)	0.392
C4 (g/l)	0.20 (0.16, 0.24)	0.22 (0.17, 0.32)	0.390	0.20 (0.16, 0.24)	0.22 (0.16, 0.32)	0.402
CFB (mg/dl)	42.55 (35.00, 48.15)	48.30 (40.40, 56.30)	0.129	42.60 (35.05, 48.90)	45.25 (35.53, 55.62)	0.246

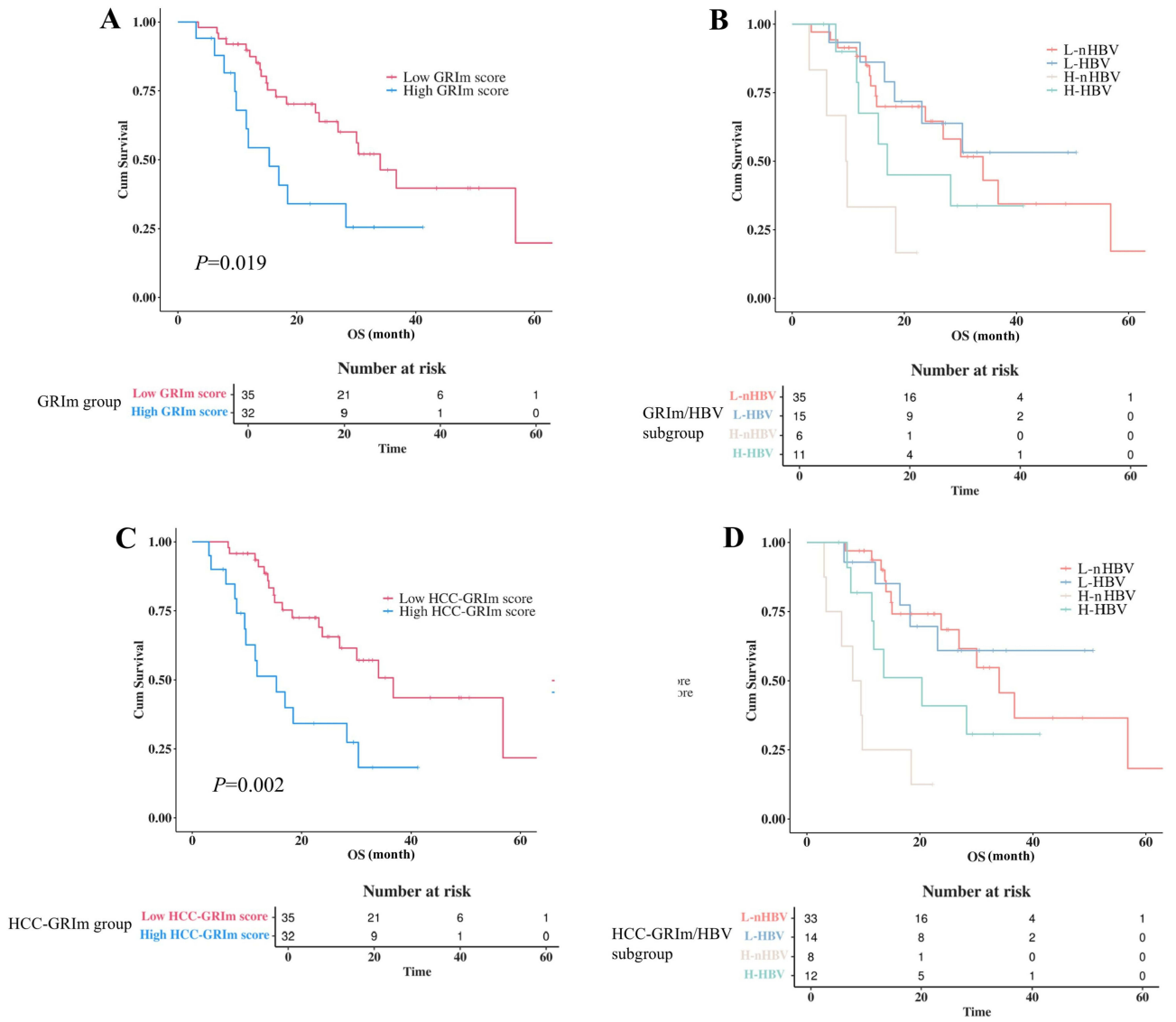

Figure 2 Kaplan–Meier curve according to GRIm score (**A** and **B**) and HCC-GRIm score (**C** and **D**). For panels (**B** and **D**), detailed P values for subgroup comparisons are provided in the Results section.

Abbreviations:: L-nHBV, low score in HBV non-activation; L-v, low score HBV activation; H-nv, high score in HBV non-activation; H-v, high score in HBV activation.

Survival Assessment According to Stratification

The optimal cut-off value for $CD3^+CD8^+$ was determined using the Maxstat method, which identifies the threshold that maximizes the separation between survival groups based on the Log Rank test. The optimal cut-off value for $CD3^+CD8^+$ cell proportion was determined to be 30.91%, based on survival analysis. Patients were stratified into $CD3^+CD8^+ >$ 30.91% and $CD3^+CD8^+ \leq 30.91\%$ groups, revealing a significant difference in OS between the two cohorts. Patients with $CD3^+CD8^+ > 30.91\%$ had markedly shorter median OS compared to those with $CD3^+CD8^+ \leq 30.91\%$ [16.5 months (95% CI: 9.8–26.9) vs 36.7 months (95% CI: 23.8–NR); $P = 0.011$, Log Rank test statistic = 6.416]. Compared with the Log Rank test based on GRIm score (P=0.019) and traditional staging (BCLC, P=27; CNLC, P=0.19), the Log Rank test based on the novel immune score ($CD3^+CD8^+$) had higher statistical significance (Figure 3).

Discussion

This study systematically evaluated the GRIm score and its modified HCC-GRIm score for their prognostic value in uHCC patients who underwent TACE plus ICIs and anti-VEGF antibodies/TKIs. The results show that both the GRIm

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Table 4 Comparison of Tumor Response in Different Scores

Variable	PD	SD	OR	*P*
Best response				
GRIm score				0.181
Low	2 (4.0)	14 (28.0)	34 (68.0)	
High	3 (17.6)	4 (23.5)	10 (58.9)	
HCC-GRIm score				0.250
Low	2 (4.3)	12 (25.5)	33 (70.2)	
High	3 (15.0)	6 (30.0)	11 (55.0)	
At first evaluation				
GRIm score				0.484
Low	6 (12.0)	15 (30.0)	29 (58.0)	
High	3 (17.6)	7 (41.2)	7 (41.2)	
HCC-GRIm score				0.131
Low	5 (10.6)	13 (27.7)	29 (61.7)	
High	4 (20.0)	9 (45.0)	7 (35.0)	

Abbreviations:: PD, progressive disease; SD, stable disease; OR, objective response.

Table 5 Tumor Response Comparison of Different Scores Based on HBV Stratification

Variable	OR	nOR	*P*
GRIm score			
Low score			0.390
HBV activation	12 (80.0)	3 (20.0)	
HBV non-activation	22 (62.9)	13 (37.1)	
High score			0.976
HBV activation	7 (63.6)	4 (36.4)	
HBV non-activation	3 (50.0)	3 (50.0)	
HCC-GRIm score			
Low score			0.640
HBV activation	11 (78.6)	3 (21.4)	
HBV non-activation	22 (66.7)	11 (33.3)	
High score			0.409
HBV activation	8 (66.7)	4 (33.3)	
HBV non-activation	3 (37.5)	5 (62.5)	

and HCC-GRIm scores can effectively predict OS in uHCC patients, with higher scores associated with significantly worse prognosis. Differences in immune indicators were observed between patients with lower and higher scores, suggesting that GRIm-related scores may serve as important indicators of systemic inflammatory and immune status, with potential implications for optimizing clinical decision-making.

The GRIm score integrates serum albumin, NLR, and LDH to capture systemic inflammation and immune status, with NLR playing a central role.[20] High NLR has been linked to immune imbalance, peripheral immunosuppression, and tumor-associated inflammation, while neutrophilia and lymphopenia may promote MDSC accumulation, suppress effector T cells, and reduce responsiveness to ICIs.[21–23] In our cohort, patients with high GRIm and HCC-GRIm scores showed significantly higher Igλ, Igκ, and IgG levels, consistent with chronic B-cell activation, abnormal humoral immunity, immune complex formation, and immune escape, which may attenuate ICI efficacy.[24–27] Although B-cell function was not directly examined, these patterns support the presence of a disturbed immune milieu in patients with high GRIm scores. Notably, however, short-term radiologic responses (PD, SD, OR) did not differ significantly between

Table 6 Univariate and Multivariate Analyzes of Factors Related to Overall Survival

Variable	Univariate Analysis		Multıvariate Analysis (1)		Multıvariate Analysis (2)	
	HR (%95 CI)	P	HR (%95 CI)	P	HR (%95 CI)	P
Age (y)	0.83 (0.39–1.73)	0.623				
Sex	0.53 (0.23–1.18)	0.12				
Child Pugh Stage*	1.39 (0.59–3.25)	0.447				
ECOG PS	2.37 (1.15–4.87)	0.018	2.70 (1.27–5.72)	0.009	3.05 (1.42–6.57)	0.004
BCLC Stage	1.49 (0.73–3.06)	0.270				
CNLC Stage *	1.43 (0.85–2.41)	0.174				
Extrahepatic spread	1.21 (0.55–2.64)	0.634				
Vascular invasion*	1.96 (0.91–4.16)	0.008				
HBV activation	0.91 (0.43–1.86)	0.788				
AFP (ug/L)	1.14 (0.54–2.46)	0.720				
Abnormal prothrombinm (AU/mL)	0.99 (0.99–1.00)	0.353				
Alkaline phosphatase (U/L)	1.00 (0.99–1.00)	0.682				
$CD3^+$ (%)	1.02 (0.98–1.06)	0.322				
$CD3^+CD4^+$ (%)	0.98 (0.95–1.03)	0.445				
$CD3^+CD8^+$ (%)	1.04 (1.00–1.07)	0.042	1.05 (1.01–1.10)	0.021	1.06 (1.02–1.11)	0.006
$CD4^+/CD8^+$ (%)	0.63 (0.37–1.06)	0.088				
$CD3^-CD\ (16^+56)^+$ (%)	1.00 (0.97–1.05)	0.619				
$CD3^-CD19^+$ (%)	0.94 (0.87–1.00)	0.068				
Igλ (mg/dl)	1.00 (0.99–1.00)	0.308				
Igκ (mg/dl)	1.00 (1.00–1.00)	0.031	0.99 (0.99–1.00)	0.898	0.99 (0.99–1.00)	0.461
C3 (g/l)	3.77 (0.09–143)	0.474				
C4 (g/l)	1.62 (0.41–6.48)	0.491				
IgM (g/l)	1.25 (0.80–1.94)	0.326				
IgA (g/l)	1.34 (1.06–1.70)	0.012	1.25 (0.89–1.75)	0.197	1.28 (0.91–1.78)	0.153
IgG (g/l)	1.06 (0.97–1.16)	0.153				
CFB (mg/dl)	0.99 (0.96–1.02)	0.503				
GRIm score#	2.51 (1.19–5.26)	0.015	2.65 (1.10–6.40)	0.030		
HCC-GRIm score#	3.28 (1.61–6.73)	0.001			4.57 (1.81–11.54)	0.001

Notes:: *Variance inflation factor (VIF) analysis showed that the VIF values for variables A, B, and C were 1.191, 2.918, and 2.627, respectively, all below the threshold of 5. This indicates no significant multicollinearity, allowing their inclusion in the multivariate Cox analysis. # Multicollinearity was assessed using the variance inflation factor (VIF) to evaluate the correlation between the GRIm score and the HCC-GRIm score. The results showed that both ZA and ZB had a VIF value of 6.67, indicating a moderate degree of collinearity (VIF > 5). As a result, multivariable Cox regression analyses were performed separately for the GRIm score [Multıvariate Analysis (1)] and the HCC-GRIm score [Multıvariate Analysis (2)].

GRIm subgroups, suggesting that GRIm may be more informative as a long-term immune-inflammatory prognostic marker rather than a predictor of early tumor shrinkage.

This study also examined the potential impact of HBV infection on the predictive ability of the GRIm score. Chronic HBV infection, a major cause of HCC, contributes to immune dysregulation by triggering persistent hepatic inflammation, activating innate immune pathways, and releasing inflammatory cytokines, which may alter peripheral neutrophil and lymphocyte counts as well as markers like LDH and ALP.[28–34] In our cohort, both the proportion of HBV activation and ALP levels were significantly higher in patients with high GRIm scores, supporting the link between HBV infection and systemic inflammatory states. Notably, elevated ALP may indicate bile duct injury or chronic cholestasis, suggesting that HBV-induced hepatic and biliary inflammation could influence inflammatory markers incorporated into the GRIm score. This finding suggests that although HBV activation may influence certain components of the GRIm score, it does not substantially impair the score's validity or prognostic utility in HCC patients. These results further indicate that the inflammatory and immune status captured by the GRIm score is not solely attributable to HBV-related inflammation but may more broadly reflect tumor–host immune imbalance. Therefore, even in the presence of HBV activation, the GRIm score retains strong prognostic performance in clinical practice. Nevertheless, future studies should involve larger sample sizes and incorporate additional variables such as viral load, antiviral treatment history, and HBV mutation profiles to

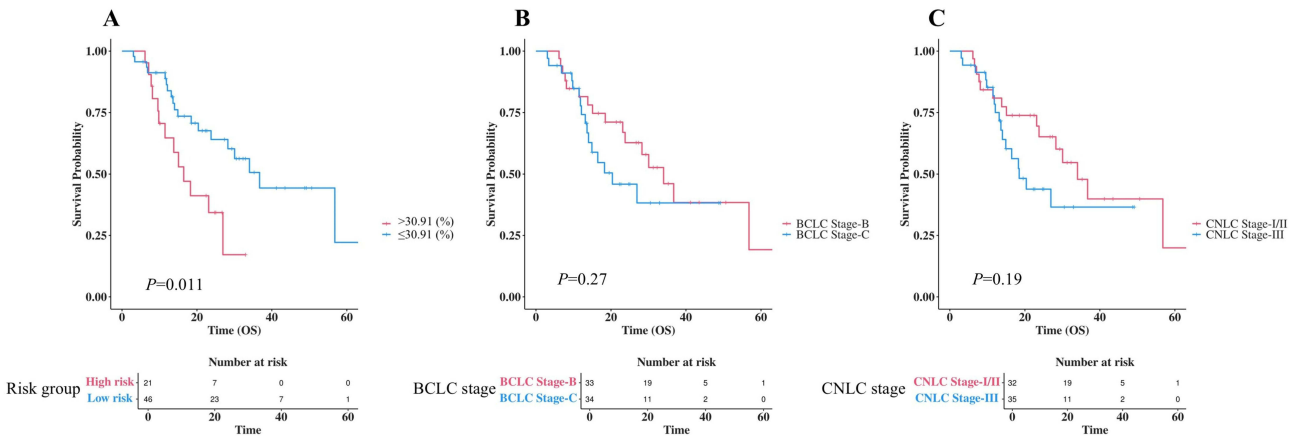

Figure 3 Kaplan–Meier curve according to $CD3^+CD8^+$ stratification (**A**), BCLC Stage (**B**) and CNLC Stage (**C**). The China Liver Cancer (CNLC) staging system categorizes HCC into stages I/II, representing early to intermediate disease, and stage III, representing advanced disease, based on tumor characteristics, liver reserve, and patient performance status. This system is widely used in clinical practice in China for prognostic stratification and therapeutic decision-making.

further clarify the extent and mechanism by which HBV infection status may influence the clinical utility of the GRIm score.

Another important finding of this study was that the proportion of $CD3^+CD8^+$ T cells was significantly associated with OS in patients. The optimal cut-off value, determined by the Maxstat method, was 30.91%, and patients with higher $CD3^+CD8^+$ levels had worse survival, which contrasts with traditional expectations. It is generally believed that higher $CD8^+$ T cell infiltration in tumor tissue indicates a better prognosis; however, in this study, elevated $CD3^+CD8^+$ levels in peripheral blood were associated with poorer outcomes. This may reflect activation-induced exhaustion or functional suppression of circulating T cells, rather than effective immune surveillance within the tumor microenvironment.[35–37] Similar patterns have been observed in HCC and other solid tumors, where an increased proportion of $CD8^+$ T cells with high PD-1 expression or other exhaustion features is associated with an exhausted gene signature and poorer survival, even though the absolute T-cell numbers are higher.[38,39] Taken together, these findings suggest that, in the setting of chronic inflammation and advanced disease, a higher proportion of circulating $CD8^+$ T cells may mainly reflect dysfunctional or terminally exhausted populations rather than effective antitumor effectors, which could partly account for the adverse prognostic impact seen in our cohort.

In this study, the CNLC and BCLC categories did not provide meaningful prognostic discrimination. Several factors may explain why CNLC and BCLC staging failed to discriminate prognosis in our cohort. First, this was a highly selected group of uHCC patients treated uniformly with TACE plus ICIs and anti-VEGF antibodies/TKIs, most of whom had preserved liver function and good performance status, which narrowed variability in tumor burden and liver reserve and blunted stage-related survival differences. Second, both CNLC and BCLC were developed and validated mainly in populations treated with surgery, TACE alone, or earlier systemic therapies; in the context of modern TACE–immunotherapy–anti-VEGF combinations, outcomes may depend more on tumor biology and host immune/inflammatory status than on anatomical stage, consistent with the independent prognostic value of GRIm, HCC-GRIm, and $CD3^+CD8^+$ T-cell proportion in our study. Finally, the modest sample size and unbalanced distribution across stages may have further reduced the power to detect survival differences between CNLC/BCLC categories.

Nonetheless, several limitations should be acknowledged in this study. First, the retrospective design inherently carries a risk of selection bias, which may compromise the generalizability of the findings. Second, the lack of longitudinal monitoring of dynamic immunological markers limits the ability to comprehensively assess the temporal evolution of the GRIm score during treatment. Future prospective studies are warranted to elucidate the dynamic changes and predictive value of GRIm scores in real-time clinical settings. Additionally, the relatively small sample size and the focus on HBV activation status, rather than a broader comparison between HBV-infected and non-infected patients, may restrict the applicability of the results. Therefore, validation in larger, prospective, multi-center cohorts is essential to substantiate these findings.

In conclusion, this study demonstrated that both the GRIm and HCC-GRIm scores are effective prognostic indicators in uHCC patients treated with TACE plus ICIs and anti-VEGF antibodies/TKIs, with higher scores significantly associated with reduced OS. Notably, their prognostic value remained robust regardless of pre-treatment HBV activation. Peripheral immune markers, including Igλ, Igκ, and IgG, were significantly elevated in patients with higher scores, reflecting systemic immune–inflammatory dysregulation. Moreover, multivariate analysis identified the GRIm score, HCC-GRIm score, and $CD3^+CD8^+$ T-cell proportion as independent prognostic factors for OS, underscoring their potential utility in risk stratification and personalized management of uHCC. In this single-center cohort, HCC-GRIm did not show clear incremental prognostic value beyond GRIm; however, this finding should be interpreted with caution given the limited sample size, and larger multicenter studies are needed to determine whether GRIm can reliably serve as a stand-alone tool or whether HCC-GRIm provides added benefit in broader clinical settings.

Conclusion

While baseline peripheral immune marker data from a subset of this cohort have been reported previously, they were not analyzed within the framework of GRIm and HCC-GRIm scoring systems.[40] By extending prior work that primarily focused on dynamic changes in circulating immune indicators, the present study integrates these immune parameters into structured GRIm and HCC-GRIm models, thereby enabling a more comprehensive assessment of systemic inflammation and immune status in uHCC patients undergoing TACE combined with ICIs and anti-VEGF antibodies/TKIs. This study demonstrates for the first time that both GRIm and HCC-GRIm scores serve as independent prognostic factors for overall survival, maintain their prognostic relevance regardless of baseline HBV activation status, and provide stratification performance that is at least comparable to conventional staging systems such as BCLC and CNLC. By shifting the focus from descriptive monitoring of immune marker dynamics to score-based prognostic modeling, the present work offers a more clinically applicable framework for individualized risk stratification in uHCC patients receiving combination therapy.

Ethics Statement

This retrospective study was reviewed and approved by the Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 2024352). Given the retrospective design, the requirement for informed consent was waived; nevertheless, written informed consent was obtained from all patients at the time of each hospital admission. Data were collected and analyzed exclusively for research purposes. The study procedures complied with the ethical principles of the Declaration of Helsinki (1975).

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Disclosure

The authors indicated no potential conflicts of interest.

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